PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference WO1042	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/000032	05.01.2005	06.01.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant
KABUSHIKI KAISHA HAYASHIBARA SEIBUTSU KAGAKU KENKYUJO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000032

Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☒ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000032

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 3, 5, 9 and part of 1, 6, 7

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 3, 5, 9 and part of 1, 6, 7

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000032

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:

   ☐ paid additional fees

   ☐ paid additional fees under protest

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

Claim 1 involves a plurality of tumor necrosis factor mutant proteins that are common to each other in binding specifically to TNF-R1 or TNF-R2, and can be divided into those having exhibiting an antagonist effect and those exhibiting an agonist effect toward tumor necrosis factor. Document JP 7-285997 A, for example, describes an agonist specifically binding to TNF-R1 and being a tumor necrosis factor mutant protein having substitution of the amino acid residue at position 86 from the N-terminus in the amino acid sequence represented by SEQ ID NO: 1 in the Sequence Listing," and therefore "binding specifically to either TNF-R1 or TNF-R2" cannot be considered a technical feature that makes a contribution over prior art. As a result, this authority finds that the tumor necrosis factor mutant proteins of claim 1 are not so linked as to form a single general inventive concept.

Claim 3 also involves a plurality of tumor necrosis factor mutant proteins that are common to each other in specifically binding to either TNF-R1 or TNF-R2 and exhibiting an agonist effect toward tumor necrosis factor. However, as described above, an agonist specifically binding to TNF-R1 and being a tumor necrosis factor mutant protein having substitution of the amino acid residue at position 86 from the "N-terminus in the amino acid sequence represented by SEQ ID NO: 1 in the Sequence Listing," was already known and therefore "binding specifically to either TNF-R1 or TNF-R2" cannot be considered a technical feature that makes a contribution over prior art. As a result, this authority finds that the plurality of tumor necrosis factor mutant proteins included in claim 3 are not so linked as to form a single general inventive concept.

The same applied to claim 5, too. (Continued in supplemental box)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. See Supplemental Box

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/000032

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1, 2, 4, 6-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1, 2, 4, 6-8	NO
Industrial applicability (IA)	Claims	1, 2, 4, 6-8	YES
	Claims		NO

2. Citations and explanations:

Document 1: US 5606023 A
Document 2: J. Biol. Chem., 1993, Vol. 268, p. 26350-26357
Document 3: Drug Delivery System, 2003, Vol. 18, p. 536-544

Based on the descriptions in documents 1-3 cited in the international search report, the inventions of claims 1, 2, 4, and 6-8 lack an inventive step.

Document 1 describes the following: (1) the binding of TNFR-p75 (TNF-R2 in this application) to TNF is linked to side effects of toxicity, (2) the binding of TNFR-p55 (TNF-R1 in this application) to TNF is linked to the cellular toxicity activity with respect to toxicity cells (column 1, etc.), and (3) when a TNF mutant that binds specifically to TNFR-p75 (TNF-R2 in this application) acts as an antagonist, it is useful in inhibiting systemic toxicity caused by TNF (column 2, etc.). In other words, it presents the motivation for obtaining a TNF mutant that is specific to one receptor and acts as an antagonist.

In this context, as described in document 2 and the like the amino acid residues of TNF involved in the specific binding to a receptor are known, and a method of efficiently screening blanket amino acid substituted mutants, for example, the "System for Creating Functional Artificial Human Proteins Using the Phage Surface Presentation Method" and the like described in document 3 (page 538, etc.), was already known. Therefore, this authority finds that persons skilled in the art can easily conceive of obtaining the "TNF mutant that is specific to one receptor and acts as an antagonist" suggested in document 1.

Document 3 describes binding a water-soluble high polymer such as polyethylene glycol to a protein to improve the stability of a physiologically active protein in the body (page 539, etc.), and this authority finds that persons skilled in the art can easily add this kind of constitution as needed.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box III, IV

Continuation of Box III

Thus, claims 1 to 9 describe 24 inventions, i.e., inventions relating to an antagonist binding specifically to either TNF-R1 or TNF-R2 and inventions relating respectively to the amino acid sequences represented by SEQ ID NOS: 37 to 59.

Continuation of Box IV

The parts of claims 1, 6, and 7 relating to tumor necrosis factor mutant proteins having an antagonist effect, and claims 2, 4, and 8.